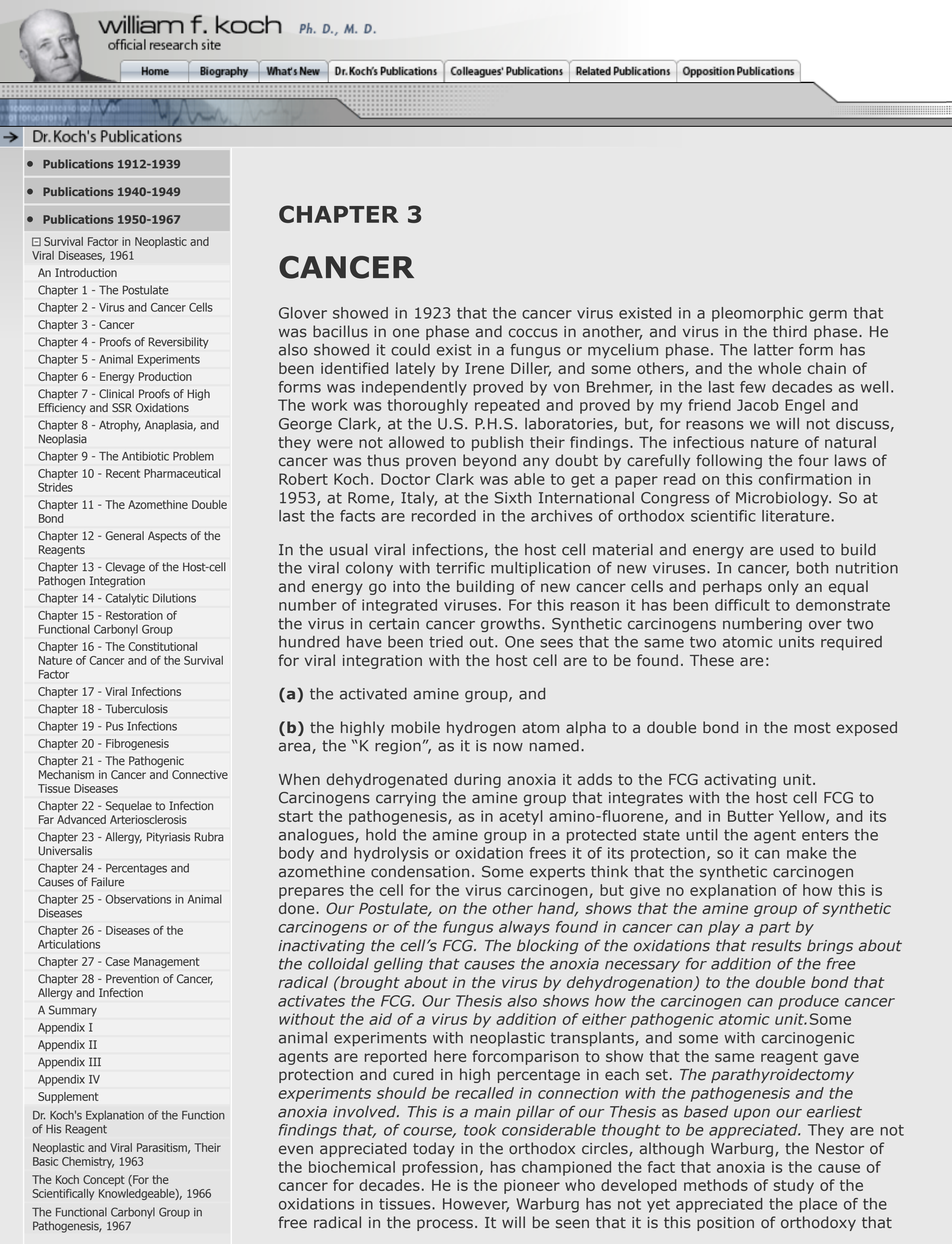




has limited progress in the explanation of the mechanism of anoxia in causing cancer, and the true nature of the carcinogenic change. Nevertheless, his contributions that won for him the Nobel Prize in Medicine on this subject are a monument of support to our Postulate. Hence we give some quotations from his most recent summary in "*Naturwissenschaften*," Vol. 42 " p. 401, 1955:

If one examines them in the light of the data we have presented in the preceding pages, it will be evident that they *confirm our own Thesis on the pathogenesis of cancer and disease, in general. They point out the essential status of anoxia, which we have claimed is necessary for the pathogen to be changed by dehydrogenation (of the tissue metabolism) to a free radical which instead of being burned and disposed of as fuel in the presence of oxygen, is not burned in its absence but is able to add to the cell grana and do so at the very point where the activation of the oxidations is generated, namely the double bonds that activate the Carbonyl group, which we credit with initiating the tissue oxidations by serving as a dehydrogenator of fuels and pathogens. Thus anoxia is essential to the pathogenesis, as it disposes the pathogen, carcinogen, virus or what not, to be able to integrate with the host cell and block grana function.* The following quotations support our Thesis as far as they go.

"One method for the destruction of the respiration of the body cells is removal of oxygen. If, for example embryonal tissue is exposed to an oxygen deficiency for some hours and then is placed in oxygen again, 50 percent or more of the respiration is usually destroyed. The cause of this destruction of respiration is lack of energy. As a matter of fact, the cells need their respiration energy to preserve their structure, and if respiration is inhibited, both structure and respiration disappear." If one estimates the amount of normal function, one sees how the pathogenesis we have described will accomplish what Warburg reports here. Again, "If an injury to respiration is to produce cancer, this injury must, as already mentioned, be irreversible. We understand by this not only that the inhibition of respiration remains after the removal of the respiratory poison but, even more, that the inhibition of respiration also continues through all the following cell divisions, for measurements of metabolism in transplanted tumors have shown that cancer cells can not regain normal respiration, even in the course of many decades, once they have lost it."

"But why are the body cells dedifferentiated when their respiration energy is replaced by fermentation energy? At first, one would think that it is immaterial to the cells whether they obtain their energy from respiration or from fermentation, since the energy of both reactions is transformed into the energy of adenosine triphosphate, and yet adenosine triphosphate = adenosine triphosphate. This equation is certainly correct chemically and energetically, but it is incorrect morphologically, because, although respiration takes place for the most part in the structure of the grana, the fermentation enzymes are found for a greater part in the fluid of the protoplasm. The adenosine triphosphate synthesized by respiration therefore involves more structure than the adenosine triphosphate synthesized by fermentation." Since the enzymes and intermediaries of fermentation, which biochemists accept as playing a big part also in the cell respiration, bathe the grana and the grana do not use them, as the quotation shows, then the conventionally accepted process is not correct, and a different process and different set of enzymes and intermediaries are involved. This process must be one, which inactivates the grana when oxygen is missing; hence the logical deduction is that the free radical is an essential part of an early intermediary as we have hypothesized for so long.

Further, "The first notable experimental induction of cancer by oxygen deficiency was described by Goldblatt and Cameron, who exposed heart fibroblasts in tissue culture to intermittent oxygen deficiency for long periods and finally obtained transplantable cancer cells, whereas in control cultures that were maintained without oxygen deficiency, no cancer cells resulted. Clinical experiences along these lines are innumerable." Warburg emphasizes, "but there is only one common cause into which all other causes of cancer merge, the irreversible injuring of respiration." He states, "In recent years it has been recognized that subnarcotic doses of urethane cause lung cancer in mice in 100 percent of treatments. Urethane is particularly suitable as a carcinogen, because, in contrast to alcohol, it is not itself burned up on the respiring surfaces and, unlike ether and chloroform, it does not cytolyze the cells. Any narcotic that has these properties may cause cancer upon chronic administration in small doses." So Warburg recognizes that a

carcinogen must be not destructible by the cell's oxidative mechanism or otherwise. It can then become integrated with the cell and become a part of it, and can become accumulative as the disposing anoxia provides occasion. Warburg states in this connection, "Any respiratory injury due to lack of energy, however, whether it is produced by oxygen deficiency or by respiratory poisons, must be cumulative since it is irreversible."

The essential nature of the process of fermentation subjects it only to control by the circumstances that control any enzyme action. These are temperature, the pH reaction of the medium, the concentration of the ferment and of the substrate. Besides such accessories as the magnesium ion or when needed, a co-enzyme will determine the speed and extent of the reaction. Fermentation progresses as well in a test tube as in a living cell. *No physiological control of these qualities for the specific service of the cell economy are known, except one, and that is the presence of the oxidation process.* Normally this is the presence or absence of oxygen. Pasteur was first to observe this relationship, and the great Warburg named it after this supreme observer, "the Pasteur Effect. This phenomenon was first described by him when observed in yeast cultures, but it is a common property to all cells that are obligatively aerobic. He reported that if a culture of yeast is deprived of oxygen, fermentation comes to the aid of the cell to supply the energy for vital processes, and if oxygen is again admitted to the culture, the fermentation ceases and oxidation takes its place. Fermentation is very wasteful and less than one-fifteenth as efficient as oxidation in the use of fuel material. *The mechanism of the Pasteur Effect has never been explained by orthodox biochemistry. However, one will see that our Postulate incorporates its explanation as a function of the Functional Carbonyl Group.*

Oxidation has several positions of control in its process in line with our Postulate. The first is the potency of the FCG, which must start the process by dehydrogenating the fuel. When this Carbonyl group is not free, as when the hydrogen it removes from the fuel is not taken away by some electron acceptor system, then oxidation is blocked. And for this, oxygen is essential as the ultimate electron acceptor in aerobic organisms. So lack of oxygen has two steps in blocking oxidation or hindering it. *Another position of control is the inactivation of the FCG by additions to the double bonds that activate it.* This would happen as we explained when anoxia prevents the free radical formed by FCG action from becoming a peroxide free radical so it must add to some position as that of the activating double bond. When this happens the FCG is inactivated and the starting of another oxidation progression is blocked. Fuels so added, may easily be burned away by the process we outlined for removal of pathogens, but normally it is not accomplished by FCG action when oxygen is again admitted unless the FCG belongs to a different unhindered structure. If a pathogen has been added the SSR is needed to free it. * However, when oxygen is lacking the FCG as a rule will not be relieved of its hydrogen atom and can not form a free radical in the fuel until oxygen is admitted, and this is a protection to the mechanism.

* The SSR is a synthetically produced Carbonyl compound of high Oxidative-Reduction potential, used as a therapeutic agent.

Physiologically, however, the control that is designed to serve the economy of the tissue itself and the organism as a whole is regulated by the need for energy production. Oxidation is regulated so quantitatively but fermentation is not. The need for energy is determined by the work to be done by a functional unit, and this is regulated by nerve or some hormone action, which releases the phosphate's stored energy to become work energy. This creates a deficit of stored phosphate energy, and oxidation must get going to replenish the supply. We explained elsewhere how the FCG accomplishes this act. So physiologically, oxidation is controlled by the need of energy for work, and the substances concerned in the process in addition to oxygen and the fuel are the FCG, creatine, and phosphoric acid. Therefore free creatine and free phosphoric acid and possibly some calcium balancing factor will give the free FCG a chance to start oxidation progressions that will yield the energy to form energy carrying creatine-phosphoric acid, as we explained before. Dehydrogenation and FCG action are concerned in oxidation only, and not in fermentation. Therefore, fermentation is probably blocked by inactivating its initiating enzyme by the act of dehydrogenation to form an active free radical in it, so that it makes an inactivating addition that is split by phosphoric acid set free when it is liberated from an energy carrying ester. The ferment would then act through its restored

hydroxyl group when energy fails, " a possibility only, as the need for energy production would be indicated by an accumulation of phosphoric acid, the first indicator for the need of fermentation, that is also able to liberate the ferment's bound hydroxyl group, that was inactivated by oxidation (dehydrogenation) during anoxia. Aside from such automatic control, there is the nerve and hormone control of the FCG and its azomethine double bond with the amine group of creatine where the nerve impulse determines its rupture to form the phosphate energy carrier, or its formation to discharge the energy load into the working mechanism. The phosphate energy bonds of fermentation are not formed or split in that way. Their energy must enter the functional mechanism through a different door. Mass action and energy transferred by photosensitization may determine such activity. There is no data on which to base a decision.

Fermentation need not be a general affair, but may be localized in some particular tissue where the FCG function is hindered. Function forced by fermentation energy beyond physiological control is the characteristic of all allergies including cancer. The type of allergy is determined by the functional unit involved, secreting fibrillae in hay fever, contractible fibrillae in asthma, conducting-synapse fibrillae in compulsion neuroses, mitotic fibrillae in cancer, etc. However, FCG block is necessary as described before. And the permanent block is done by a condensation with a firmly bonding amine as guanidine, or of some virus or an amine produced by decarboxylase action on some amino acid. When Victor C. Vaughan demonstrated in 1910 that the alkaline hydrolysis of various proteins gave rise to a toxic fraction that caused anaphylaxis, the writer was privileged to work in this kindly scientist's laboratory and isolated several toxic amines from his alkaline hydrolysate. They produced the allergic changes of fatal anaphylaxis. Later on it dawned on the writer that if his Postulated FCG were blocked by toxic amines produced in a tissue by their decarboxylases that operate best in an alkaline medium, fermentation would be the result that could force the allergic responses that occur in anaphylaxis, and the type of response would depend upon the functional unit acted upon, while the amount of amine could be very small.

To check up on this a large number of allergy cases were treated with the SSR by the writer and several hundred collaborators. The results reported were about 85% recoveries obtained on one or two doses. These included the intractable asthmas and hay fever cases as well as the infantile eczemas that fail to respond to known methods. Some guinea pigs sensitized to egg white by the Vaughan method were also treated with success, but such experiments are not determinative unless all variables can be excluded, and they cannot. At any rate, one sees here the practical meaning of *the Pasteur Effect* as modified by a pathogen. Physiologically, fermentation stops in an anoxic tissue when oxygen is admitted, but here pathologically, the use of oxygen was blocked until the hindrance to the FCG was removed by use of a "super" Carbonyl group, the SSR. Though in orthodox biochemistry the explanation of the Pasteur Effect has not yet been made, we see that the Carbonyl group is the key to the situation both normally and in pathological processes. *Our Postulate is thus strengthened by its broad utility.*

That the narcotic action promotes neoplastic behavior is only too well known to the clinician. Especially is this true of the oxides of nitrogen that present permanent free radicals that can block respiration and promote cancer growth most disastrously. Their essential action is to hinder cell respirations. Other confirmatory quotations in support of our Postulate could be given, but this is enough.

While it was important to recognize the essential role of oxygen lack in carcinogenesis, the observation is of no practical use until one understands the mechanism whereby the anoxia disposes to neoplasia. *It is too bad that Warburg was not aware of our findings after parathyroidectomy, the action of high-energy amino groups in attacking the oxidation initiating Carbonyl group of the grana as we Postulated, and that thereby the oxidation mechanism was blocked. It is too bad he gave no thought to the position of the free radical formed by these dehydrogenations and the absolute need of molecular oxygen to carry the oxidation progression forward, and that when the substrate acted upon could find no oxygen to combine, it must combine an appropriate double bond, and thus integrate with the cell's energy producing mechanism. It is too bad that he did not make these steps and then the third step to recognize that the very integration of the pathogen with the host cell invited the oxidative separation of both leaving the*

host cell in good functional status, while the pathogen was destroyed. He therefore missed the essence of the reversibility of carcinogenesis, and the means of bringing it about.

We will give the details as we go along, and the substantiating proof for each step. However, what Warburg did establish was a great advance in cancerology and his prestige as a biochemist makes this support to our Thesis, a most valuable one.